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Simultaneous Control of Central and Helical Chiralities: Expedient Helicoselective Synthesis of Dioxa[6]helicenes

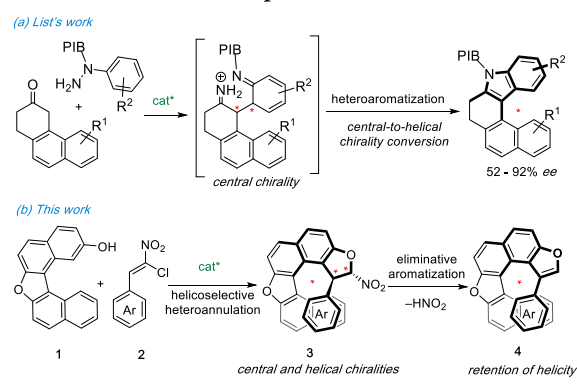
Peng Liu, Xiaoze Bao, Jean-Valère Naubron, Sara Chentouf, Stéphane Humbel, Nicolas Vanthuyne, Marion Jean, Laurent Giordano, Jean Rodriguez,* and Damien Bonne*

ABSTRACT: An expedient synthesis of a new family of configurationally stable dioxa[6]helicenes was established using a sequential helicoselective organocatalyzed heteroannulation/eliminative aromatization via enantioenriched fused 2-nitro dihydrofurans featuring both central and helical chiralities. Starting from simple achiral precursors, a broad range of these previously unknown chiral heterocyclic scaffolds were obtained with good efficiency, and their aromatization proceeded with very high enantiopurity retention in most cases.

Helicenes are *ortho*-fused polycyclic aromatic compounds angularly arranged in a more stable screw-shaped conformation resulting in an inherent helical chirality.¹ Compared to carbohelicenes,² the presence of one or more heteroatoms in a chiral nonracemic helix induces structural modifications, significantly affecting their configurational stability and usually resulting in enhanced or more specific properties. Hence, heterohelicenes have been revealed as promising scaffolds for numerous recent developments, such as catalyst design and their utilization in enantioselective reactions,³ molecular recognition,⁴ material sciences, including cryptography,⁵ light-emitting devices,⁶ spin filters,⁷ molecular machines,⁸ and some biologically active agents.⁹ However, these developments are hampered because of the lack of general synthetic approaches to optically active derivatives, and only a few direct metal-catalyzed approaches have been proposed within the past decade.¹⁰ Therefore, the design of innovative and widely applicable enantioselective strategies to access new families of chiral nonracemic π -conjugated heterohelicenes is highly desirable.

In 2014, List's group reported the first and still unique enantioselective organocatalytic approach to azahelicenes (Scheme 1a).¹¹ This elegant chiral phosphoric acid-catalyzed (CPA) enantioselective Fischer's indole synthesis probably involves a central-to-helical chirality conversion through the transient generation of two sp^3 -stereogenic centers. The following heteroaromatization leads to a series of new configurationally stable nonaromatic indolohelicenes with moderate to good enantioselectivities. On the basis of our recent interest in the synthesis of axially chiral 3-arylfuran atropisomers,¹² we devise a new expedient helicoselective access to hitherto unknown helically chiral fused furans (Scheme 1b). We thus reasoned that the use of an extended aromatic bis-nucleophile **1** in combination with a chloronitroalkene **2**, in the presence of a bifunctional organocatalyst (cat^*), would give the centrally and helically chiral fused dihydrofuran **3** through an unprecedented helicoselective Michael/O-alkylation heteroannulation sequence. The follow-

Scheme 1. Enantioselective Organocatalytic Approach to Azahelicenes and Our Proposal to Dioxahelicenes



ing aromatization by elimination of nitrous acid would provide the corresponding dioxa[6]helicene **4** with conservation of the helical chirality.

The required helical configurational stability is anticipated to be secured by a remote steric effect of the bulky aryl group at the 3-position of the furan ring of both **3** and **4**, ensuring increased barriers to diastereo- and enantiomerization, respectively.¹³ In the case of helical dihydrofuran **3b** ($R = H$), this crucial effect is clearly described by our DFT calculations, showing a kinetically affordable but thermodynamically impossible diastereomerization (Figure 1). Indeed, the diastereomer (P,S,S)-**3b** with an inverted helix is 40 kJ/mol

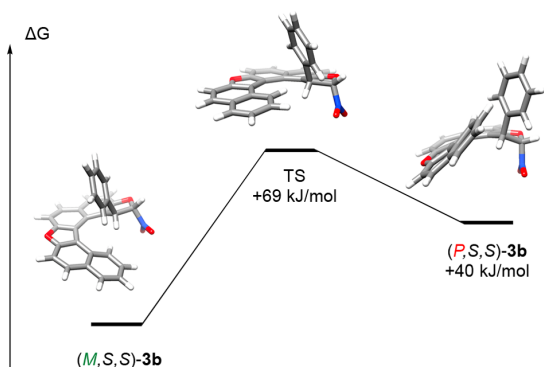


Figure 1. Computed diastereomerization of 3b.

less stable than the (*M,S,S*)-3b, with a transition state at only 69 kJ/mol. Hence the “return barrier” from (*P,S,S*)-3b to (*M,S,S*)-3b is as small as 29 kJ/mol, arguing for the totally helicoselective formation of (*M,S,S*)-3b upon heteroannulation.

In the case of the targeted dioxo[6]helicenes 4, the importance of the remote steric effect is corroborated by comparison of their configurational stability with the corresponding carbo[6]helicene (Figure 2). The presence of

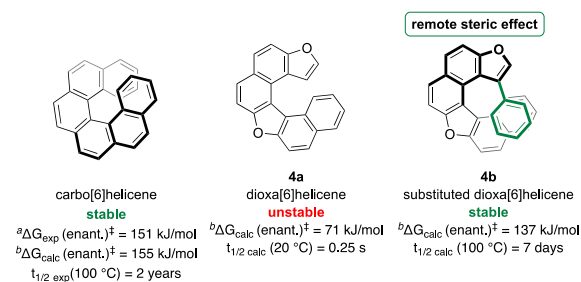
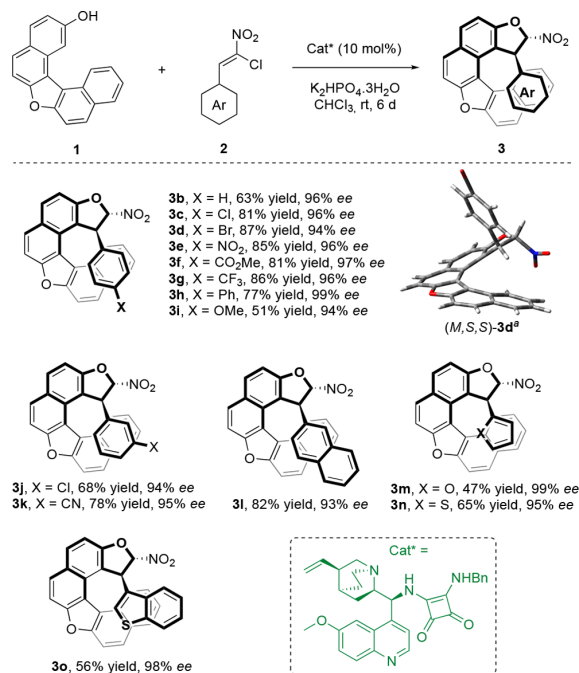


Figure 2. Barriers to enantiomerization for carbo[6]helicene and representative dioxo[6]helicenes 4a,b. ^aExperimental value.¹⁶ ^bCalculated values with the PBE0 DFT method.

two five-membered furan rings results in a more open helical pitch¹⁴ responsible for a much lower barrier to enantiomerization of $\Delta G^{\ddagger} = 71$ kJ/mol for configurationally labile unsubstituted dioxo[6]helicene 4a compared to the experimental $\Delta G^{\ddagger} = 151$ kJ/mol that we computed at $\Delta G^{\ddagger} = 155$ kJ/mol for stable carbo[6]helicene.¹⁵ Gratifyingly, a strong beneficial remote steric effect of the phenyl substituent at the 3-position of the furan ring in 4b increases the barrier to enantiomerization up to $\Delta G^{\ddagger} = 137$ kJ/mol, corresponding to a half-life of about 7 days at 100 °C, arguing for a high configurational stability.

With these encouraging observations validating our initial conceptual approach, we started our investigations using dinaphthofuranol 1¹⁷ as the bis-nucleophile with chloronitroalkene 2b (Ar = Ph) in the presence of the bifunctional quinine-derived squaramide organocatalyst, and the use of weak base (K_2HPO_4 , 2 equiv) was necessary to trap HCl formed *in situ* (Scheme 2, Cat*). We were delighted to observe the smooth formation of the desired dihydrofuran 3b in 63% yield and 96% ee, and only one diastereomer could be detected in the crude reaction.

Scheme 2. Reaction Scope for the Dihydrofuran Synthesis



^aSimulated structure of 3d.

With optimized reaction conditions in hand (see the Supporting Information for details), we next explored the generality of this new domino organocatalyzed helicoselective synthesis of dihydrofurans 3. Substituents at the *para*-position of the phenyl ring were all compatible with this protocol as well as a naphthyl group, affording the corresponding products with excellent stereocontrol (3c–i and 3l, 93–99% ee), even if the yield was moderate in the case of the 4-methoxyphenyl group (3i, 51% yield). Substituents in the *meta* (3j,k) position of the phenyl ring were also tolerated with slightly diminished yield, but again, excellent enantioselectivities were observed. Chloronitroalkenes bearing heteroaryl rings such as furan, thiophene, and benzothiophene behave with comparable efficiency, with good yields and excellent enantioselectivities (3m–o).

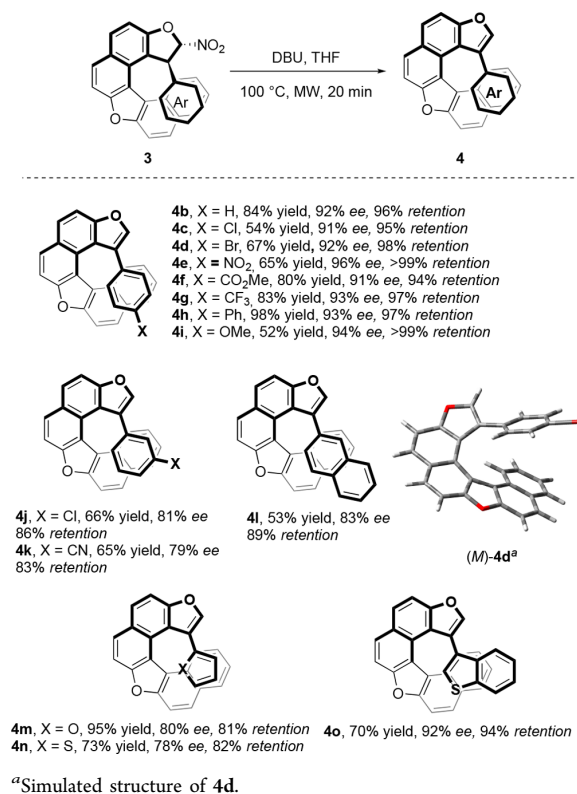
To ascertain the expected helicoselectivity resulting in the simultaneous control of central and helical chiralities, we needed an accurate assignment of the relative and absolute configurations of the chiral dihydrofurans. Because no exploitable crystals could be obtained, we tackled this key point by a complete chiroptical spectroscopy study with 3d combining vibrational and electronic circular dichroisms (VCD and ECD) with density functional theory (DFT) calculations (see the Supporting Information for details).¹⁸

A good agreement between experimentally recorded VCD and ECD spectra of 3d and the simulated VCD and ECD spectra of the (*M,S,S*)-3d enantiomer allowed the determination of the absolute configuration of 3d as (*M,S,S*).

To the best of our knowledge, this represents the first example of simultaneous control of central and helical chiralities by a catalytic chemical transformation¹⁹ offering unprecedented chiral platform molecules for the synthesis of a new family of heterohelicenes.

For this endeavor, we next explored the aromatization step, via a simple base-promoted elimination of HNO₂.²⁰ After a short optimization (see the [Supporting Information](#) for details) the use of DBU as a strong organic base in THF at 100 °C for 20 min under microwave irradiation was required. Most importantly, under such relatively harsh conditions, the aromatization proceeded with very high enantiopurity retention in most cases, leading to a broad range of highly configurationally stable dioxo[6]helicenes ([Scheme 3](#)).

Scheme 3. Scope of the Synthesis of Dioxo[6]helicene

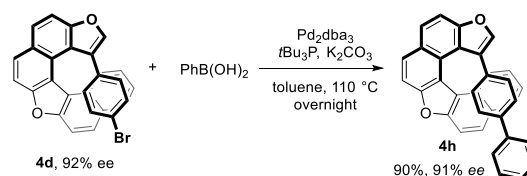


A simple phenyl group (**4b**) or *para*-substituted aryl groups (**4c–i**) are suitable, affording good to excellent yields as well as excellent retention of the helical stereogenic information (94–100% retention). The presence of a substituent in the *meta* position or a 2-naphthyl group gave the corresponding products (**4j–l**) in good yields but with slight erosion of the enantiopurity (79–83% ee). Interestingly, smaller heteroaryl groups such as furan and thiophene could be introduced at the peripheral region of the final helicene (**4m** and **4n**, 80% ee and 78% ee, respectively) with a more efficient helical retention for the bulkier benzothiophene (**4o**, 92% ee).

The same complete chiroptical spectroscopy study (VCD, ECD, and DFT) with **4d** as model compound allowed the definitive determination of its absolute configuration as (*M*)-**4d** (see the [Supporting Information](#) for details).

Considering the high configurational stability of dioxo[6]helicenes **4**, we are confident that they could serve as synthetic scaffolds for further post-transformations. This is illustrated by converting **4d** to the biphenyl derivative **4h** via Suzuki cross-coupling reaction with phenyl boronic acid ([Scheme 4](#)).

Scheme 4. Synthetic Transformation of 4d

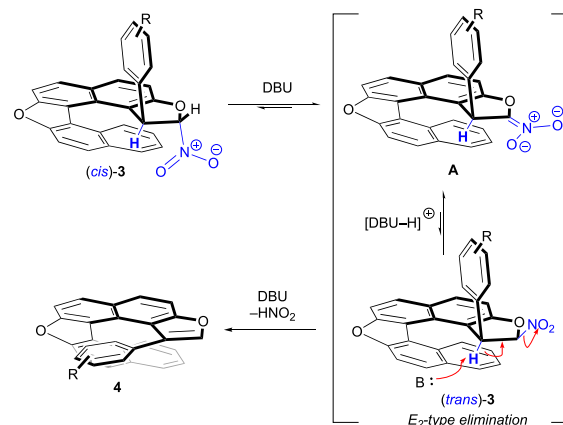


Expectedly, **4h** was isolated in excellent yield, and the enantiopurity was retained even after prolonged time at 110 °C, accounting for a very high barrier to enantiomerization for this class of compound.

From a mechanistic point of view, the aromatization with conservation of the helical chirality raises some questions whether it follows a *syn*- or an *anti*-elimination (*E_i* vs *E₂*). First, the recent base-promoted atroposelective aromatization involving a *syn*-elimination of HNO₂ at room temperature²¹ was discarded, because DBU at room temperature or up to 60 °C was revealed to be inefficient (see the [Supporting Information](#) for details). Moreover, in a control experiment, compound **3c** was heated in toluene (MW, 100 °C, 30 min) without DBU leaving it unchanged, which also excludes a thermal *E_i* elimination.

With these experimental observations, an alternative base-promoted *E₂*-type mechanism was envisaged. The *cis* relative configuration between the nitro group and its β-hydrogen atom in (*cis*)-**3** ([Scheme 5](#)) would then require a prior

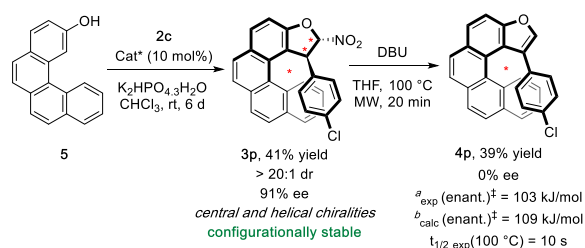
Scheme 5. Mechanism for the DBU-Promoted *E₂*-Elimination



epimerization to (*trans*)-**3** via nitronate intermediate **A**. Compound (*trans*)-**3** would subsequently undergo a rapid aromatization via DBU-promoted *E₂*-elimination of HNO₂.

Finally, as an even more challenging goal, we tried to use the present method for the enantioselective synthesis of oxa[5]helicenes ([Scheme 6](#)). Hence, from benzo[*c*]phenanthren-2-ol **5** and **2c** in the presence of the bifunctional organocatalyst (*cat**), we were delighted to observe the helicoselective formation of **3p** in 41% yield as a single diastereomer with high enantiopurity (91% ee). This shows that the remote steric effect of the *p*-chlorophenyl group is powerful enough to bring configurational stability even to oxa[5]helicenes, with similar diastereomerization profile as compared with **3b** (see the [Supporting Information](#), p SI-104). The following aromatiza-

Scheme 6. Toward Oxa[5]helicenes



^aExperimental value.¹⁶ ^bCalculated values with the PBE0 DFT method.

tion step allowed access to the desired oxa[5]helicenes **4p** (39% yield), albeit with complete racemization, under these conditions (100 °C, 20 min). Its relatively low barrier to enantiomerization experimentally determined at 103 kJ/mol (see the [Supporting Information](#)) and confirmed by theoretical calculations ($\Delta G_{\text{calc}}^\ddagger = 109$ kJ/mol, see the [Supporting Information](#)) explains the fast racemization under these reaction conditions. Further investigations are needed to increase the enantiomerization barrier of this appealing family of oxa[5]helicenes.

In conclusion, we have developed an expedient synthetic access to a new family of configurationally stable dioxo[6]-helicenes from simple achiral precursors. The helicity is created and controlled during an organocatalyzed domino Michael/C–O alkylation step, which delivers 2-nitrodihydrofurans featuring both two stereogenic carbon atoms and an helical shape. Interestingly, this represents the first case of a catalytic chemical transformation in which both central and helical chiralities are controlled simultaneously from simple achiral substrates. The required configurational stability, even in the challenging oxa[5]helicene series, is secured by a remote steric effect ensuring kinetically affordable but thermodynamically impossible diastereomerization. This approach offers unprecedented chiral platform molecules for the synthesis of enantioenriched heterohelicenes by simple base-promoted elimination of HNO₂ with excellent conservation of the helical information in most cases.

Calculation Details. All the calculations were performed with Gaussian²² at the PBE0/def2TZVP//PBE0/def2SVP level²³ and included the “GD3” Grimme correction for the dispersion.²⁴ Hence, a single-point energy calculation with the def2TZVP basis set was performed on top of a PBE0/def2SVP optimization and frequency calculation.

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Notes

The authors declare no competing financial interest.

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